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COMPARTMENTAL MODELS FOR TRACE METALS IN MAMMALS

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ABSTRACT

Kinetic models for the distribution and elimination of certain trace metals in mammals allow evaluation of metal burdens in critical target organs under time-variables exposure patterns, and thus may assist in formulating exposure standards. The linear compartmental model is described and some of its implications for conceptual models of trace metal metabolism are developed. The model is then applied to data on multiple doses of cadmium in mice. Many trace metals do not follow simple linear kinetic models because exposure to more than one metal simultaneously often results in synergistic effects.

INTRODUCTION

Compartmental models for the absorption, distribution, and excretion of trace substances in animals have been widely used in certain areas of health physics, particularly in the evaluation of hazards from radionuclides such as the alkaline earth metals [1]. The use of such methods in risk assessment for community exposures to nonradioactive toxic metals is surprisingly less common. Conceptual models can be formulated, but there are important theoretical and practical problems in applying such models to risk assessment.

MODEL FORMULATION

An organism may be divided into a number n of distinct subunits or compartments labelled $j=1,2,\dots,n$; the external environment into which some of the trace metal may be eliminated is denoted by $j=0$. The rate coefficient at which material flows from compartment j to compartment h is denoted $k(h,j)$. There are m external sources of the trace metal, e.g., food, air, water, cigarette smoke, and for laboratory experiments the routes of administration of the substance. Each external source is labelled $i=1,\dots,m$. The rate of absorption from source i into compartment j is denoted $a(i,j)$. The state of the environment is measured by the concentration

$C(i,t)$ in source i at time t . The response of the organism is measured by the mass of trace substance in compartment j at time t , denoted $X(j,t)$. Where no confusion results we may use $X(j,t)$ as the fraction of injected dose. The usual linear compartmental model expresses the evolution of $X(j,t)$ by a system of coupled linear differential equations:

$$\frac{dx(j,t)}{dt} = \sum_{h=1}^n k(h,j) X(h,t) + \sum_{i=1}^m a(i,j) C(i,t) \quad (1)$$

The unknown constants $k(h,j)$ and $a(i,j)$ may be estimated from observations at several time periods on the contents of some of the compartments. These hypothetical compartments may not be directly observed or even observable, and the observation may combine the contents of several conceptually distinct compartments e.g. "blood" data combines both plasma and red blood cells, and "kidney" data combines both the renal cortex and medulla. For individual metals different organs may be critical to toxicity.

The solution to equation (1) will (usually) have the form of a mixture of exponential terms [2]:

$$X(j,t) = \sum_{h=1}^n b(h,j) \exp(-v(h) t) \quad (2)$$

The coefficients $b(h,j)$ are explicit functions of the absorption coefficients $a(i,j)$, the concentrations $C(i)$ or doses injected (assumed constant), and the eigenvectors of the rate coefficient matrix $(-k(h,j))$. The important time scale parameters $v(j)$ are eigenvalues (i.e., characteristic values or roots) of the rate coefficient matrix, and thus must be the same for each compartment j . The whole-body retention function $R(t)$ is thus also a mixture of exponentials:

$$R(t) = \sum_{j=1}^n X(j,t) = \sum_{h=1}^n \sum_{j=1}^n b(h,j) \exp(-v(h) t) \quad (3)$$

The constants are then estimated from data e.g. by an iteratively reweighted least squares computer program such as SAAM distributed by the National Institutes of Health [3]. Of course, it is not that easy in practice.

PROBLEMS IN COMPARTMENTAL MODELLING

Each fitted compartment constitutes a unit or pool of readily exchangeable molecules and may not coincide with a single identifiable physiological organ within which trace metal concentration is measured. An example is the three compartment model fitted by Rabinowitz et al. [4] to lead metabolism in man. The first compartment includes both the blood lead and lead in some soft tissues, the second includes most of the soft tissue lead and some lead in soft bones, and the third compartment is mainly bone but may include other hard tissues that retain lead for a long time. However, trace metals are highly organ-specific and so the fitted pools can usually be identified with some organ of the animal.

Many investigators have fitted mixtures of exponentials to concentrations $X(j,t)$ in various compartments, but have failed to appreciate the implication of equations (2) and (3) that the exponential decay coefficients or time-scales $v(j)$ must be the same for all compartments. That is, the equation (1) is a global model for a network of interacting or communicating compartments and the solution to (1) is a global solution with the same decay constants for all compartments. This is not always easy to observe because the patterns of absorption and exposure contained in the coefficients $b(h,j)$ may provide high weight to some exponential coefficients $v(h)$ in one compartment, but more weight to other coefficients $v(j)$ in some other compartment. This is almost inevitable in systems in which a large number n of compartments contribute a large number n of time-scales $v(j)$. One example of this is given by Matsubara-Khan for long-term retention of cadmium in mice following a single subcutaneous injection of cadmium chloride [5]. For each j a two-compartment open model

$$X(j,t) = u(j) (\exp(-v(j) t) - \exp(-w(j) t)) \quad (4)$$

was fitted with different values of $v(j)$, $w(j)$ for each j ; e.g. for blood, $v=0.024$ and $w=0.65$; for liver, $v=0.011$ and $w=0.57$; for kidney, $v=0.0007$ and $w=0.30$; for salivary gland, $v=0.0016$ and $w=0.73$ (v, w units of day⁻¹). Quite apart from questions of the statistical adequacy of the fitted curves and the precision of the estimated parameters (both capable of considerable improvement), this approach is not theoretically tenable because different v and w values were used for each compartment.

Different structural models may yield solutions that fit the data equally well. This is not just a problem in statistical precision of the data. Even if the data were completely free of intrinsic variability, it would not be possible to identify the structure of a model with many compartments, not all of which can be observed or loaded with an administered dose of trace metal. This is well known to theoreticians, but has not been recognized by biologists. The situation has been summarized by Wagner [6]. Even if a linear compartmental model fits the data, there is likely to be a different and equally plausible linear compartmental model

that fits the data just as well. Thus, when a linear compartmental model is appropriate, it is usually not necessary to be concerned about which particular model is to be used since the model cannot be uniquely identified in any event. On the other hand, if a nonlinear kinetic model is appropriate, it is necessary to specify the correct model in order to make accurate predictions. In practice, the choice of a model can never be reduced automatically to selection of the one that minimizes some statistical goodness-of-fit criterion. There must always be consideration of biological plausibility of the proposed model.

An enormous variability occurs in physiological parameters among the animals within any population, even among homogeneous inbred strains of laboratory animals. Occasionally authors do not even report the strain of laboratory animal used, even though there are well documented differences in absorption and distribution of trace metals such as lead among different strains of rats and mice [30]. Differences, abundant in the literature, are emphasized by references that contain vivid graphical exhibits of variability. Individual data points for cadmium concentrations in various organs of ICR mice are shown by Matsubara-Khan for a single CdCl_2 injection [5], and accumulation from extended oral intake [7]. Horner and Smith [8] plot daily cumulative excretion for two different rats. Burch and Walsh report whole-body "half-lives" of cadmium in 5 dogs of 260, 333, 388, 500, and 1046 days, and similar orders of variation in tissue concentrations among four of these dogs (F, G, H, I) after 20-21 days [9]. Among human populations, McLellan et al. [10] observed cadmium retention after the washout of a chromium marker indicated the end of observational confounding from stomach contents; absorption of an oral cadmium dose varied from 1.5% to 16.2% among 14 healthy subjects. Welinder et al. [11] studied a sample of 11 high-frequency solderers in Sweden; the whole-body cadmium half-times varied from 25 to 66 days in 10 of them, but the last had a Cd half-time of 146 days. After an outbreak of mercury (Hg) poisoning in Iraq, the whole-body Hg retention half-times of a sample of the victims were found to vary from 37 to 189 days [12]. Finally, Rabinowitz et al. [4] found that the time-scales $1/k(1,2)$ for soft-tissue washout of lead from four men were 28, 28, 35, and 51 days.

Even though the kinetic parameters of both experimental and natural populations are broadly distributed, only mean (sometimes median) concentrations in organs or tissues are commonly reported. That this practice results in errors by those who predict effects on populations is an absolute mathematical fact (e.g., by applying Jensen's inequality): Time scales estimated from population-averaged concentrations must be shorter than the average of that time-scale parameter over the same population. This is, again, not merely a problem of statistical uncertainty. The conclusion is that the best studies are single-subject studies in which the model is fitted to each subject individually. Because the determination of tissue concentrations in experimentally exposed laboratory animals requires their sacrifice, only a single time-point is available for each animal. Even so, it would be helpful

to show published data points with labels for each individual animal for all organs autopsied. It would also be helpful to design the experiment from the beginning so as to use animals that are genetically similar, perhaps from the same litter or related litters. This would improve the precision of the fitted model, but would provide less information about the distribution of kinetic parameters within a genetically dissimilar population.

In most studies there appears to be inadequate attention to control of metabolic and dietary factors that may modify the rate coefficients over time. Many dietary factors can affect the absorption of metals [13]. For cadmium, the quantity of other metals in the diet is important because some metals present in the kidney and liver may induce the formation of metal-binding proteins that bind cadmium, mercury, and other metals tightly in the renal cortex. Vitamins also affect metal metabolism. Deficiencies of essential metals such as zinc, iron, and calcium affect not only metabolism but also ad libitum diet; e.g., calcium deficiency in humans may cause excessive consumption of lead-bearing materials as diet supplements [14]. There has been practically no consideration of simultaneous modelling of several metals with different exposure patterns. Where they have been used, biochemical models for metabolic interaction of metals appear complex [15].

The misspecification of model structure may be less important than the failure to correctly model nonlinear kinetic mechanisms. When concentrations of Cd and other metals are low, cadmium kinetics appear linear. When metal concentrations are high, there is an induced formation of metal-binding proteins and corresponding change in some of the linear rate parameters $k(h,j)$. There is an apparent saturation of these proteins and an eventual increase in cadmium excretion in urine when cadmium concentrations in the renal cortex become sufficiently high. Thus the constant-coefficient compartmental models for cadmium start to fail when they are most needed to predict the onset of damage to renal tubules.

Similarly, the linear kinetic models that have been fitted to lead data in animals and humans may not be adequate to describe low-level long-term exposures that are of particular relevance to community health. Blood lead provides a measure of short-term exposures, but most of the lead absorbed (at least 90% of the body burden for long-term exposures) ends up in the bones and hard tissues. This long-lived pool of lead may be mobilized long after exposure ceases. Lead retained in bone and hard tissue appears to have a power-law retention function rather than the mixture of exponentials in equations (2) and (3). The retention function proposed by the International Commission on Radiological Protection for the alkaline earth metals Ca, Sr, Ba, Ra [1] is:

$$R(t) = (1-p) \exp(-mt) + p[a \exp(-vt) + (1-a) \exp(-wt)] (t+c)^{-b} \quad (5)$$

No linear linear compartmental model with a finite number of compartments can generate such a model. Very long term lead studies in beagle dogs [16] suggest that equation (5) is also a good description of lead retention, which is plausible in view of the similarity of lead to the alkaline earths. Diffusion has been suggested as the mechanism for lead transport in bone, but an attempt to model calcium exchange at bone surfaces using one particular diffusion mechanism was not successful [17]. Another approach has been developed and applied to long-term lead retention in beagle dogs [18]. The diffusion equation is first solved for the canalicular territory in the bone, which is assumed to be cylindrical in shape. Then only the eigenvalue spectrum of the diffusion equation solution is needed to approximate the bone by a finite number of components. It is quite practical to estimate unknown constants from the data. However, little data has been published on long-term low-level effects of many other trace metals.

Another possible source of nonlinear kinetics is the route of administration of the trace metal. There appear to be some differences in the handling of inorganic lead and lead in organic compounds, e.g. tetraethyl lead as used in gasoline additives. It may thus be necessary to set up separate submodels for each carrier and route of administration. Thomas et al. [19] compare many routes of cadmium administration among several species. Physiological models of such systems may require saturable processes governed by Michaelis-Menten kinetics, or may be flow-limited or diffusion-limited.

The extrapolation of animal studies to people is always a problem, and in the case of trace metal toxicology the extrapolation cannot be done at all because of the lack of a single accepted structural model with the same list of rate coefficients for all species. There may be processes that simply do not extrapolate well. For example, Suzuki and Taguchi [19] report that the highest concentration and greatest retention of Cd in two monkeys who received a single oral dose of CdCl_2 was in the upper small intestine wall and in the content of the small intestine, suggesting that intra-intestinal circulation was qualitatively far more important in primates than in rodents. Comparisons of studies with different species should be interpreted with caution.

A final concern is the use of whole-body retention half-times as a criterion, particularly for mouse-to-man extrapolations. The implication of the compartment model is that there is a spectrum of n time scales $v(1), \dots, v(n)$, and that by altering the temporal pattern of exposure one alters the weights $b(h, j)$ in each compartment and thus the relative importance of the time scale in that compartment. This is particularly important when the critical target organs may have a very different response pattern than does the whole organism. Atmospheric pollutants such as carbon monoxide show a highly variable exposure pattern [20,21], but trace

metals have not been as thoroughly studied. And if the kinetic process is significantly nonlinear, e.g., lead retention from equation (5), then the half-time concept is nearly meaningless.

Sometimes no model provides a good fit for all parts of the data, and it is necessary to settle for a simple description of some part of the data. This is often done by fitting straight lines to $\log X(j,t)$ vs. t over some observed range of t values [15,18]. This technique is not recommended because the generally subjective choice of the range of t values over which a curve is to be approximated by a straight line in essence defines the slope of that line. If some simple smooth approximation to the organ retention curves is needed, the use of exponential splines [23] is recommended. Unfortunately, purely descriptive models of this sort have limited value for prediction of concentrations in unobservable critical target organs.

MODEL APPLICATION TO CADMIUM

A number of multicompartment models have been considered for cadmium metabolism in mammals, including Shank, Vetter, and Ziemer [24,25], Kjellstrom and Nordberg [26], and Marcus [27]. I Shank et al. proposed a 9-compartment model to fit their data on mice (see [27], Fig. 1). Kjellstrom and Nordberg proposed an 8-compartment model for cadmium metabolism in man, fitted primarily to whole-body and kidney burdens obtained from autopsies ([26], Fig. 1). I proposed a 13-compartment model that provides a greatly improved fit to Shank's mouse data [27]. The Marcus model uses plasma as a central compartment, with 7 peripheral compartments; blood, liver, and kidney each contain a compartment that exchanges rapidly with blood, and a peripheral compartment with much slower turnover of cadmium (see [27], Fig. 2). There are fecal, urinary, and biliary excretion pathways. The Marcus model is rather similar to the much more complex model for zinc metabolism proposed by Foster et al. [28], even though it is known that cadmium and zinc turnover are quite different [29]. I attempted to fit Shank's data with the Kjellstrom and Nordberg model, but the quality of fit was rather poor. An improved model is given. The model parameters in Table 1 provide a better fit to the data than those in [27]. The model presented here includes an additional peripheral blood compartment (so modeling both red blood cells and metal-binding proteins in blood) as well as a somewhat reliable estimate of the long-term kidney retention parameters.

The results for Shank's data are compared for 2 models in Table 1. Male adult mice of the SW/NIH strain received three injections of cadmium acetate and were sacrificed in groups of 4 at 15 time points. In a second experiment [25] the injections contained zinc as well as cadmium, in a 100:1 weight ratio. The cadmium dose of 0.0833 μg in an injection of 0.1 ml was below any toxic effect level. The effects of simultaneous zinc exposure are particularly evident in the much more rapid flow of cadmium from the rapid-exchange compartments in blood and liver to

the slow-exchange compartments. Most other cadmium distribution processes appear to be slowed by zinc administration, including the flow from blood to liver, from blood to kidney, and blood to gastrointestinal tract. The fecal excretion from liver is slightly faster; this interesting small pathway seems to be reliably estimated and may tentatively be considered as related to biliary excretion.

A 9-compartment model was also fitted to long-term mouse retention data by Matsubara-Khan [5]. The Kjellstrom-Nordberg model proved much less satisfactory than the Marcus model, but neither model provided a really adequate description of the data. The substantial variations in concentration observed among the 10 mice at each time point may have been in part responsible for the unsatisfactory statistical fit due to the rate averaging problem described in the preceding section. The results are shown in Table 2.

TABLE 1

Values of kinetic parameters for short-term exposure of mice to cadmium

Rate parameters $k(i,j)$ in units of day^{-1} were estimated by the SAAM 27 program. Statistically significant differences for zinc-exposed mice are denoted by *. SS is the residual sum of squares, in (percent of dose)². Estimated standard errors are in parentheses.

Cadmium flow	Cadmium only		Cadmium + Zinc	
From/to	Shank SS=3688	Marcus SS=1.79	Marcus SS=1.50	
Blood plasma/cells	---	32.9 (1.4)	109 (4.6)	*
Blood cells/plasma	---	46.5 (2.4)	79.7 (3.8)	*
Plasma shallow/deep	---	0.104 (.017)	0.007 (.009)	
Plasma deep/shallow	---	1.10 (.06)	0.060 (.126)	*
Blood/liver	950.4	391 (8.6)	283 (6.5)	*
Liver/blood	2.30	-1.23 (.14)	0.68 (.10)	*
Liver shallow/deep	---	3.66 (1.28)	6.99 (3.62)	
Liver deep/shallow	---	9.65 (1.54)	19.24 (2.24)	*
Blood/kidney	96.48	32.8 (1.02)	32.7 (0.96)	
Kidney/blood	2.02	0.716 (.046)	0.905 (.066)	*
Kidney shallow/deep	---	0.058 (.019)	0.254 (.025)	*
Kidney deep/shallow	---	0.036 (.014)	0.028 (.018)	*
Blood/pancreas	43.2	12.9 (.38)	10.5 (.26)	*
Pancreas/blood	2.88	0.778 (.042)	0.549 (.027)	*
Blood/spleen	4.32	1.98 (.09)	1.29 (.05)	*
Spleen/blood	5.45	2.53 (.17)	1.31 (.09)	*
Blood/testes	3.60	1.36 (.05)	1.12 (.05)	*
Testes/blood	3.02	1.12 (.06)	1.01 (.07)	
Blood/carcass	561.6	293.4 (7.5)	313.3 (7.9)	
Carcass/blood	6.05	2.83 (.13)	2.91 (.13)	
Blood/GI tract	345.6	89.6 (1.7)	80.5 (1.8)	*
GI tract/blood	8.64	3.17 (.12)	2.42 (.12)	*
Liver/feces	---	.0372 (.0052)	.0571 (.0078)	
Blood/feces	1.04	8.07 (.76)	5.85 (.75)	
Blood/urine	0.14	1.94 (.54)	3.44 (.54)	

Data from Shank, Vetter, and Ziemer [24,25]

TABLE 2

Values for kinetic parameters for long-term exposure of mice to cadmium

Cadmium flow From/to	Parameter day ⁻¹	Std. Error day ⁻¹	
Blood/liver	1.41	0.13	
Liver/blood	0.001	0.0030	
Liver shallow/deep	0.160	0.0081	
Liver deep/shallow	0.037	0.0056	
Blood/kidney	1.51	0.13	
Kidney/blood	0.026	0.007	
Kidney shallow/deep	3.56	0.91	
Kidney deep/shallow	0.0049	0.0030	
Blood/carcass	5.10	0.58	
Carcass/blood	0.053	0.0046	
Blood/stomach	0.024	0.0049	
Stomach/blood	0.020	0.0071	
Liver/feces	0.162	0.0083	By GI tract
Blood/feces	0.001	0.0039	Other excretion
Blood/urine	0.079	0.130	

Cadmium data from Matsubara-Khan [5]

CONCLUSION

There are many practical and conceptual problems in the use of compartmental models to study bioavailability of trace metals in organs of mammals. The examples for cadmium show that appropriate application of compartmental models to suitable data sets can produce reliable estimates of the organ distribution of trace metals and can quantify the changes in distribution parameters that result from simultaneous exposure to other metals. Successful applications of compartmental models are more likely when: (1) experimental animals are biologically very similar so that average organ concentrations have small relative variation and are truly representative of organ concentrations in each individual animal; (2) observations are available in enough peripheral tissues that very little of the total body burden is not accounted for; (3) the number and range of sacrifice times covers most of the spectrum of exponential time scales; (4) the modeller recognizes kinetically distinct unobserved pools or compartments within physiological organs, since the kinetic parameters can often be inferred when the preceding conditions are met. Finally, even the failure of linear compartmental models to fit the data may be useful if the failure helps to identify nonlinear biological mechanisms.

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